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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: [Docket No. 99N-1737]
Notice: Public Availability of Information on Clinical Trials for Investigational Devices Intended to Treat Serious or Life-Threatening Conditions

Dear Madam or Sir:

The enclosed comments are being submitted by Baxter Healthcare Corporation, CardioVascular Group, in response to the Food and Drug Administration's Request for Comments to the *Federal Register* notice dated June 22, 1999 (Volume 64, Number 119). Baxter's CardioVascular Group (CVG) is a leader in providing a comprehensive line of therapies and services to treat late-stage cardiovascular disease. Marketed cardiovascular devices include heart valves, vascular grafts, cardiac monitoring catheters, cardiopulmonary bypass equipment and devices, and left ventricular assist systems. Many of these devices are intended to treat serious or life-threatening conditions.

CVG's basic position: CVG is deeply concerned that the proposed publicly available data bank will have a negative impact on innovation and rapid medical device development in the U.S. due primarily to the loss of confidentiality of intellectual property. However, if medical device information is to be included, posting of clinical trial information should be strictly voluntary. Further, specific information posted should be at the discretion of the sponsor to protect trade secret information, and information to be posted should be reviewed in advance by the affected investigators and institutional review boards.

CVG respectfully submits these comments to FDA.

Sincerely,

Patricia L. Garvey, Ph.D.
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99N-1737

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Comments on Public Availability of Information on Clinical Trials for Investigational Devices Intended to Treat Serious or Life-Threatening Conditions

1. *Is there a public health need for the inclusion of device investigations within the scope of the data bank under 402(j) of the PHS Act?*

   It is unclear whether a specific public health need exists for inclusion of device investigations within the scope of the data bank. The data bank could conceivably facilitate study enrollment. Study enrollment rate may be affected in part by limited availability of information about the trial and therefore might be accelerated by including this information in the proposed data bank. Enrollment of subjects during a clinical trial of an investigational device intended to treat a serious or life-threatening condition can be slow in some circumstances and can ultimately delay the public availability of a marketed safe and effective therapy option. However, within the limits of current IDE regulation, recruiting for subjects through public announcement is now available to investigators and sponsors on a voluntary basis. Baxter CVG believes this currently available mechanism to recruit subjects is sufficient, as this can be applied to the local geographic area where the studies are being conducted. Local recruitment has the greatest opportunity to attract locally-available subjects, thus enhancing study management and minimizing potential "lost to follow-up."

2. *If there is a public health need, what category of device trials should be made publicly available and how should this category be defined? FDA's treatment IDE regulation applies only to devices for which no comparable or satisfactory alternative exists. Should a data bank for the IDE's be similarly restricted? Should the trials that become part of the data bank include feasibility/pilot trials or only studies that are intended to demonstrate reasonable assurance of safety and effectiveness?*

   The medical device industry is innovative, fast-paced and highly competitive. Success is typically a function of rapid, well-controlled development and first to market. Firms go to great lengths to protect confidentiality of device research and development, and provide detailed information on this development to FDA under an IDE with confidence that this information is protected from public disclosure under the regulations. Most often a device firm will conduct a single IDE trial for support of a markeing application. Clinical trial investigators are routinely required to provide

markeing application. Clinical trial investigators are routinely required to provide written agreement of nondisclosure, as the clinical protocol provides critical and detailed strategic elements of the firm's research and development plan. These elements include description of the device design, intended use/indication for use, identification of the target population, and all eligibility criteria defined. As listed in the *Federal Register* notice, data elements to be provided in the databank would include confidential and proprietary information in the form of a device description, eligibility (i.e., inclusion and exclusion) criteria for patients, location of trial sites, and an investigational site point of contact.

Currently, promotion of investigational devices is prohibited under IDE regulation 21 CFR 812.7. In an attempt to recruit either investigators or subjects, sponsors can announce publicly that a clinical study is being conducted if no claim is made that the device is safe and effective for the purposes for which it is being investigated. However, this recruiting practice is voluntary and highly dependent upon agreement with the investigator and prior review and approval by the associated IRB. Inclusion in the databank should therefore be voluntary and subject to investigator and IRB review and approval.

Pilot trials are typically conducted at a minimum number of sites with very few patients (less than 20). The purpose is to assess the feasibility of conducting and safety and effectiveness trial in the target population. However, FDA may place significant restrictions on the target population for enrollment in the feasibility phase. For example, the patients may be higher risk than those targeted for the safety and effectiveness trial. The device pilot trial is, therefore, not analogous to a drug phase 1 trial that is performed with healthy volunteers and should not be included in the databank.

Many devices designed to treat serious or life-threatening conditions require concomitant surgery. The device itself may be implantable. Investigators must document study-specific skills and training and often require additional training by the sponsor as a requirement for participation in the clinical trial. In those cases where only a few investigational centers are qualified to participate in the trial (e.g., open-heart centers trained for LVAD implantation), potential patient candidates may seek to participate in trials well outside their immediate geographic location. They may agree initially to return for all required follow-up visits, however, there is evidence that many patients do not return and become "lost to follow-up" due to difficulties in traveling to the investigational sites. This can have a significant effect on the overall integrity of the study and can prolong the completion of the study and submission of the marketing application. Posting a listing of all investigational sites on a website can draw subjects from many geographic locations that may not be well served by the investigation and may increase the likelihood of lost to follow-up patient enrollment. For this reason, when sites choose to use public announcement as a recruiting tool, it is restricted to the

immediate geographic location. Investigational sites should therefore not be identified on the databank website.

3. *Investigational device trials have historically been smaller in numbers of subjects and numbers of investigational sites than investigational drug trials. What impact, both positive and negative, would the release of information have on these device trials, the sponsors, the investigators, the investigational sites, and the patients? Will a public data bank create pressures to increase the size of device trials or number of sites in situations where such expansion may increase risk to patients?*

4. *IDE information is generally protected from public disclosure under FDA regulations. If public disclosure were voluntary, would disclosure by one sponsor put pressure on sponsors of similar investigations to disclose the existence of their studies against their better judgment? Is this in the interest of public health?*

   Device firms typcally conduct a single safety and effectiveness trial to support a marketing application. If two or more firms are developing similar products and one discloses the existence of their study by posting this information on the data bank, the other firms will likely post their information as well against their better judgment for fear that the initially disclosing firm will be viewed by the market as more innovative and "first to the market" through its clinical investigation. For the small firm with a single product, this could have a negative effect on continued funding through venture capitalists, particularly if they are not first to post the information on the data bank website. As stated earlier, first to market is often associated with market success and share as well as being perceived by the market as most innovative.

5. *If disclosure is mandatory, is it likely to hamper innovations and investment in research and development? Would disclosure of these investigational device trials help or hinder research by increasing patient enrollment?*

   Mandatory disclosure is likely to hamper innovations and investment in research and development due to the nature of device development. That is, trade secrets are protected throughout a very rapid development cycle. Mandatory disclosure of strategic research and development elements, as well as financial disclosure requirements recently imposed, will continue to drive medical device research offshore where no such regulatory requirements exist. Because foreign data can be used to support marketing applications, there are increasingly more incentives to do research outside the U.S.

6. *Because sponsors can recover some of the costs of the device research and development under the investigational device regulations, should FDA be concerned that publicly available information concerning investigational device trials will result in undue financial pressure or incentives on the trial sponsor to add subjects to the trials without appropriate*

consideration of risk? Should FDA be concerned about the possibility that improper promotion and commercialization will occur as a result of a public data bank for IDE trials?

7. *Will public disclosure of information about device trials for products to treat serious or life-threatening diseases or conditions affect reimbursement policies of third party payers?*

Third party payors may see an opportunity to start influencing sample size upwards for purposes of determining reimbursement. However, the purpose of the IDE trial is to determine safety and effectiveness of a device for its intended use. Sample size requirements for an IDE trial are significantly lower than that for a economic study, and it should be the sponsor's decision alone to combine or not combine these two purposes. Health outcome studies for devices are not under FDA purview, but if IDE trial information is publicly disclosed, third party payors may exert pressure on sponsors during trials to include outcome measures or move to withhold reimbursement.

8. *What other important information or issues should the agency consider?*

- **Definitions are essential for "serious, life-threatening conditions," and differences should be clarified and relationships identified by FDA between these definitions and significant/nonsignificant risk, class II and III, and treatment use IDE criteria.**

- **How will the databank be maintained and by whom? Who will ensure its integrity? How long will information remain on the databank, and how will up-to-date information be assured?**

- **From a retrospective view, which currently commercially available devices would have been identified for inclusion in this databank?**

- **The public health need is best served by bringing good, innovative medical devices of the highest quality to the market quickly at the lowest cost. The fastest, cheapest, most controlled trials are conducted at the smallest number of sites with the fewest number of patients determined to meet preestablished primary study endpoint criteria. How would prolonging such trials, increasing their costs and potentially losing some control over larger studies (that are harder to manage, monitor and audit) better serve the public health need?**

- **How could this disclosure of information possibly <u>not</u> have a negative influence on small or start-up device companies?**

- **Device trials typically are not blinded. In many, the control is a surgical procedure. Using information obtained from the databank, patients will pursue participation in a trial and be motivated by assuming that they will be treated with the investigational device. Patients may refuse to participate in randomized trials for this reason. But even if they agree to participate and then are randomized to the control, patients may then refuse to participate and seek another opportunity at another site identified on the databank website to improve their chances for being "randomized" to the treatment arm. This will add study bias to the patient selection thus jeopardizing the study results.**

- **Inclusion in the databank of the device description, eligibility of patients, and location of sites reveal critical strategic elements of the sponsor's research and development and marketing plans. This also provides proprietary, trade-secret information to competitors.**